REMARKS

I. Summary of Office Action

Claims 37-84 are pending and under examination. Applicants elected macrocyclic lactones as the PKC activator and Alzheimer's Disease, as the disease in response to the Examiner's species election requirement.

a. Claims 37-84 are rejected under the judicially-created doctrine of obviousness type double patenting over the claims of several of the Institute's commonly-owned, co-pending applications or issued patents.

b. Claims 37-84 stand rejected as allegedly not enabled by the specification.

c. Claims 37-84 stand rejected al allegedly obvious over Choi et al. (JP 201250481), or Tamura et al., (JP 06279311), in view of Zhang et al., *Cancer Research.* 1995; 56: 802-808, and U.S. Patent No. 6,043,270 to Driedger et al.

II. Response to Office Action

By this amendment, claims 37, 39, 49, 52, 53, 65, 68, 69, 81 and 84 have been amended for clarity, to delete subject matter, or to correct dependency in view of cancelled claims. Claims 48, 51, 64, 67, 80, and 83 have been cancelled. No new matter has been added.

a. Obviousness-Type Double Patenting

Claims 37-84 are rejected under the judicially-created doctrine of obviousness-type double patenting over the claims of several of the Applicant's commonly-owned, co-pending applications or issued patents. The Examiner alleges that the presently pending claims, although not identical, are not patentably distinct over claims in U.S. Patent No. 6,825,229 ("the '229 patent"), which covers a method of treating Alzheimer's Disease and other Diseases with bryostatin-1, and pending U.S. Application Serial No. 11/802,824, which covers a composition for reducing neurodegeneration and preventing the loss of cognitive ability by administering a combination of a PKC activator and a PKC inhibitor.

In response to the rejection over the '229 patent, submitted herewith is a terminal disclaimer. Applicant request that the rejection over Application Serial No. 11/802,824 be held in abeyance until such time as claims in that application or this application are allowable.

b. Claim Rejections Under 35 U.S.C. §112—Enablement

Claims 37-84 stand rejected as allegedly not enabled by the specification. The Examiner contends that, while the application enables use of bryostatins and neristatins as the macrocyclic lactones, it does not reasonably enable use of *all* macrocyclic lactones to decrease soluble Aβ-40 and soluble Aβ-42. The Examiner relies on the unpredictability of the pharmaceutical arts and the diverse biological properties of different compounds to support his contention that it would require undue experimentation to ascertain whether other macrocyclic lactones would be effective in the claimed method.

We do not agree that undue experimentation would be required to determine whether a macrocyclic lactone is effective. The test for enablement is whether one reasonably skilled in the art could make or use the invention from disclosures in the specification coupled with information known in the art without undue experimentation. *United States v. Telectronics, Inc.*, 857 F.2d 778, 785 (Fed. Cir. 1988). If a statement of use in the specification contains within it a connotation of how to use, and/or the art recognizes that standard modes of administration are known and contemplated, the enablement requirement is satisfied. *In re Johnson*, 282 F.2d 370, 373, (CCPA 1960); *In re Hitchings*, 342 F.2d 80, 87 (CCPA 1965); *see also In re Brana*, 51 F.2d 1560, 1566, (Fed. Cir. 1993). Moreover, when a compound or composition claim is limited by a particular use, enablement of that claim should be evaluated based on that limitation. *See In re Vaeck*, 947 F.2d 488, 495, 1444 (Fed. Cir. 1991); MPEP 2164.01(c).

The present application satisfies the foregoing criteria for enablement. The specification discloses precisely how to ascertain whether a compound, including a macrocyclic lactone, might decrease soluble Aβ-40 and soluble Aβ-42. Such *in vitro* and *in vivo* experiments are routine for person of ordinary skill in the art, and are easily adaptable for high throughput screening of many compounds. See, for example, paragraphs [0098-0101], [0105-0115] and [0119-0120] of the published application 2007-0037871.

Moreover, the specification makes it clear that the macrocyclic lactone is a PKC activator, thereby narrowing the class of compounds. The specification discloses methods of determining PKC activation at, *e.g.*, paragraph [0114], although methods of determining PKC activation *in vitro* and *in vivo* are well known in the art as well.

The specification explicitly discloses or incorporates by reference a number of macrocyclic lactones contemplated for use. The fact is that there is not an "immense range and potential of number of species" of macrocyclic lactones as the Examiner alleges (Office Action page 4). The specification provides enough guidance to allow one of ordinary skill in the art to practice the full scope of the claimed invention without undue experimentation. However, even a significant amount of experimentation does not necessarily equate to *undue* experimentation. As noted above, *in vitro* experiments are routine for person of ordinary skill in the art, and are easily adaptable for high throughput screening of many compounds. "In the chemical arts, the guidance and ease in carrying out an assay to achieve the claimed objectives may be an issue to be considered in determining the quantity of experimentation needed." MPEP §2164.06.

c. Claim Rejections Under 35 U.S.C. §103—Obviousness

Claims 37-84 stand rejected al allegedly obvious over Choi *et al.* (JP 201250481), or Tamura *et al.*, (JP 06279311), in view of Zhang *et al.*, *Cancer Research.* 1995; 56: 802-808, and U.S. Patent No. 6,043,270 to Driedger *et al.*

This rejection is respectfully traversed because the Examiner has failed to establish *prima facie* obviousness. To establish a case of *prima facie* obviousness, the Examiner must 1) identify a reason why a skilled artisan would have made the claimed invention from combined the teachings of the cited references; and 2) provide evidence that skilled artisan would have a *reasonable expectation of successfully* making and using the claimed invention, based on the teachings of the cited references, *i.e.*, the result must be *predictable.* The rejection of the claims as obvious in view of Choi *et al.* or Tamura *et al.* in view of the secondary references—Zhang *et al.*, and Driedger *et al.*— fails to satisfy any of these three requirements for *prima facie* obviousness.

First, neither Choi *et al.* nor Tamura *et al.* teach macrocyclic lactones, let alone

bryostatins or neristatins, or methods for decreasing soluble Aβ-40 or Aβ-42 using these compounds. The abstract of Choi *et al.* merely suggests that a subclass of aminobenzamides—known PKC activators—may be useful in the treatment of Alzheimer's Disease. Tamura *et al.* merely suggest that a very specific structural class of PKC activators, phosphoserine fatty acid conjugates, may be useful in the treatment of Alzheimer's Disease. No examples in either Choi or Tamura show that the compounds have any therapeutic effect (the only examples show that some of the claimed compounds activate PKC). Neither Zhang *et al.* nor Driedger *et al.* cure this defect. Zhang *et al.* discuss bryostatin-1 in the context of cancer treatment **and not** Alzheimer's Disease therapy. Dreidger discloses that certain non-tumorigenic, non-inflammatory derivatives of seven classes of known PKC activators or inhibitors (including bryostatins), that have been modified at the hydroxylmethyl or 1-hydroxyethyl positions known to confer biological activity, may be useful for treating Alzheimer's Disease and a myriad of other diseases in which PKC activation or inhibition would be beneficial. Driedger does not suggest to use bryostatin derivatives over any of the other six classes to treat *any* of the diseases, let alone Alzheimer's Disease specifically. In other words, Driedger provides no "blaze marks" from which one of ordinary skill in the art would specifically select the disclosed bryostatin derivatives to specifically treat Alzheimer's or enhance learning and memory, over any of the other diseases mentioned. Importantly, Driedger provides no data showing that any of the two specifically disclosed bryostatin derivatives (compound xiii, Example 94, and compound xv, Example 96) even activate PKC, let alone reduce toxic beta-amyloid.

Second, instead of viewing the references in their entirety and the teachings as a whole, the Examiner improperly selects specific teachings from the cited references. Although the Examiner asserts that Driedger *et al.* discloses use of bryostatin-1 to treat learning and memory defects including Alzheimer's Disease, this is not the case, as explained above. Driedger actually discloses that the *non-inflammatory* PKC agonists among the compounds of his invention may useful for treating Alzheimer's Disease and numerous other diseases, but Dreidger does not explicitly suggest using the bryostatin-1 derivatives to treat Alzheimer's Disease. Moreover, as Driedger explains elsewhere, unmodified bryostatin-1 is **not** a non-inflammatory compound. Thus, when viewed in its entirety, Driedger *et al.* actually teaches away from the claimed method of improving cognitive function using bryostatin-1, and any of the PKC-activating compounds that are not modified as disclosed by Dreidger.

Third, a finding of *prima facie* obviousness requires predictability, *i.e.*, a reasonable expectation of success. This has been reaffirmed by the Supreme Court in *KSR, Int'l. v. Teloflex, Inc.*, as recognized by the U.S.P.T.O in its Examination Guidelines for Determining Obviousness Under 35 U.S.C. 103 in View of the Supreme Court Decision in *KSR International Co. v. Teleflex Inc.* (Fed. Reg. Vol. 72, No. 195, October 10, 2007). For all of the reasons discussed above, one of ordinary skill in the art would not have had a reasonable expectation of success of reducing toxic betay-amyloid by substituting a macrocyclic lactone, such as bryostatin, for the PKC activators disclosed in Choi *et al.* and Tamura *et al.* that are stated to be useful for treating Alzheimer's disease (even assuming, *arguendo*, these was a requisite reason to do so). Choi and Tamura do not show any therapeutic activity of their non-macrocyclic lactone compounds. One certainly would not have expected success by substituting the two specifically disclosed modified bryostatin derivatives of Dreidger (even assuming, *arguendo,* these was a requisite reason to do so), which have been modified at the position that is thought to be responsible for biological activity (col. 17, ll. 26-29), and which have not been demonstrated to have *any* effect on PKC.

Moreover, the Federal Circuit, post-KSR, has addressed obviousness of chemical compounds. "A prima facie case for obviousness for a chemical compound still, in general, begins with the reasoned identification of a [prior art] lead compound." *Eisai Co. v. Dr. Reddy's Laboratories, Ltd.*, 533 F.3d 1353, 1359 (Fed. Cir. 2008). Obviousness can then based on structural similarity along with some "motivation that would have led one of ordinary skill in the art to select and then modify a known compound (*i.e.* a lead compound) in a particular way to achieve the claimed compound." *Id.* Although the motivation to modify the prior art can come from many different fields, some motivation is needed. In chemical cases, this motivation may be proved by showing a "sufficiently close relationship" between the prior art and claimed compound that would "create an expectation . . . that the new compound will have similar properties to the old." In other words, an obvious substitution would be "predictable."

It therefore follows that use of unrelated compounds is also unpredictable. Structurally unrelated compounds, while possibly having some similar properties or functions in common, will certainly not predictably have undisclosed properties in common. Simply because Choi

and/or Tamura's unrelated compounds may also activate PKC does not permit the inference that these compounds will have the claimed effects on soluble beta-amyloid.

Further, in light of disclosure by Dreidger, who discloses that bryostatin-1 is a *pro-inflammatory, toxic* agonist (col. 12, l. 59 to col. 13, l. 12, and col. 13, ll. 46-50), bryostatin-1 would be predicted to be contra-indicated in Alzheimer's Disease, because Alzheimer's Disease is characterized as an inflammatory disease. Further evidence of the unpredictability among unrelated classes comes from the Examples in the present application. Paragraph [00113] of the application as-filed shows the difference in Aβ toxic peptide secretion using compounds from two different structural classes of PKC activators, benzolactam and bryostatin-1. Benzolactam and related lactam compound LQ12 had no effect on Aβ-42 secretion (*i.e.,* did not reduce the Aβ-42 toxic peptide), whereas bryostatin-1 significantly reduced production of Aβ-42 (see also Figures 12-14). According to the Examiner's reasoning, if substitution of different classes of PKC-activating compounds were reasonably predictable, there should have been no difference between the lactam compounds and bryostatin-1 on secretion of Aβ toxic peptide. Because this is incorrect, so is the Examiner's obviousness rejection.

Further, because bryostatin-1 is also known to be a PKC inhibitor, and, as of the date of the invention, was the subject of clinical trials to examine its efficacy as an anti-tumor agent based on its *inhibition* or down regulation of PKC, this makes the contemplated use of bryostatin-1 as a PKC activator for reducing beta-amyloid completely unpredictable.

Lastly, the Examiner is essentially opining that any compound that is a PKC activator will predicatably be an effective therapeutic to reduce beta-amyloid. This is akin to saying that it would be obvious that any compound that inhibits cell division would be an effective therapeutic to treat cancer. This is not the standard for obviousness. Although the Supreme Court, in *KSR*, stated that obvious to try may be obvious in some cases, this holding is limited to instances where there are a *finite* number of possibilities, and where the outcome would be *predictable*. As explained above, neither of those conditions is present—there are not a finite number of (PKC-activating) macrocyclic lactones, and it certainly was not predictable from the prior art of record or the knowledge in the art that macrocylic lactones would reduce toxic beta amyoid in subjects in need thereof. It bears repeating that the only prior art references that show *any* asserted

therapeutic effects of any of the disclosed compounds are Dreidger, who show *in vitro* anti-HIV and anti-cancer effects of several compounds from the non-bryostatin class (Examples 111-117) and Zhang, who disclose that bryostatin-1 had anti-cancer activity in mice leukemia models. None of these effects suggests that macrocyclic lactones would effectively reduce toxic beta-amyloid *in vivo*, as presently claimed.

In view of the foregoing, withdrawal of this rejection is respectfully requested.

EXCEPT for issue fees payable under 37 C.F.R. § 1.18, the Director is hereby authorized by this paper to charge any additional fees during the entire pendency of this application, including fees due under 37 C.F.R. §§ 1.16 and 1.17 which may be required, including any required extension of time fees, or credit any overpayment to Deposit Account No. 13-3250, reference No. 17357.01001. This paragraph is intended to be a **CONSTRUCTIVE PETITION FOR EXTENSION OF TIME** in accordance with 37 C.F.R. § 1.136(a)(3).

If the Examiner finds that a telephone conference would further prosecution of this application, she is invited to contact the undersigned at 202-835-7553.

Respectfully submitted,

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